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DATE: April 17, 1978

SUBJECT: Application for an experimental Use permit to test MON-8000 as a plant growth regulator on sugarcane and an application for temporary tolerances of Glyphosate on sugarcane. 524-EUP-45 PP#8G2060, PP#8H5179 (Glyphosate) Caswell#661A (Sodium N-(phosphonomethyl) glycine)

FROM: William Dykstra, Ph.D WJD 4/17/78
Toxicology Branch

TO: Libby Zink
Special Registration Section
Room 315(d)

Petitioner: Monsanto Agricultural Products Co.
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166

Tolerances established inder 40 CFR 180.364

Chemistry Branch Considerations: See page 6

Recommendations:

1. In previous reviews questions or criticisms were raised with certain studies which have not been addressed by the petitioner (memo 10/4/77, Dr. Quaife) (A) In the Ames-type in vitro test for mutagenicity of N-nitrosoglyphosate. (1) What are the actual amounts of the nitroso compound and of the positive control chemical (which are expressed as "microliters") used on test, or per plate? (2) Was an adequate quantity of N-nitrosoglyphosate tested so that, even if it were of considerably less mutagenic potency than the positive control chemicals used, it could have yielded a positive result?

B. In the mouse dominant-lethal mutagenicity test on N-nitrosoglyphosate (conducted by Industrial Biotest) the very low intraperitoneal doses of the nitrosamine used (5 & 10 mg/kg) relative to the rat oral LD_{50} of the N-nitrosoglyphosate (5000-7000 mg/kg) are questioned.

C. The teratology study on N-nitrosoglyphosate in the rabbit conducted by Industrial Biotest is judged unacceptable. If repeated, it should use larger test doses, some of which are demonstrated to be toxic to the maternal rabbit. Also at least 3 dose levels and a positive control should be used.

2. Toxicology Branch considers any quantity of N-nitrosoglyphosate which may occur in foods to be not toxicologically significant (memo of 3/6/78, Dr. Gessert)

3. Toxicology Branch finds that the EUP and the requested temporary tolerances adequately supported by available toxicology data on glyphosate. It should be noted that most supporting studies (Subacute, Chronic, reproductive, teratology, carcinogenicity and mutagenicity) on glyphosate are from IBT. These studies have to be validated or repeated.

4. Prior to registration, the questions and criticisms in this and previous reviews must be addressed by the registrant, since Toxicology Branch has in the past recommended against registration or the establishment of permanent tolerances for glyphosate.

5. The Acute toxicity studies by Younger Labs must be validated.

Proposed temporary tolerances

2.0 ppm of glyphosate and its metabolite in or on sugarcane.

0.1 ppm of glyphosate and its metabolite in or on liver and kidney of cattle, goats, hogs, horses, poultry and sheep.

Temporary Food Additive Tolerance

15.0 ppm of glyphosate and its metabolite in molasses.

Name of Product: MON-8000
Total quantity proposed for Use: 1150 lbs of product which contains 862.5 lbs A.I.

Time period: Sept. 1, 1978 to Sept. 1, 1980

Acreage: 1150 Acres in four states

Product: MON-8000

Ingredient	Percent Weight
sodium-N -(phosphonomethyl) glycine	75.0
Inerts	25.0

Inerts cleared under 40 CFR 180.1001.

A. Previously Submitted Toxicology Data

I. Acute Data

1. Acute Oral LD_{50} (rat) (rabbit)	EPA Accession No. 94176
2. Acute Dermal MLD (rabbit)	EPA Accession No. 94176
3. Skin Irritation (rabbit)	EPA Accession No. 94176
4. Eye Irritation (rabbit)	EPA Accession No. 94176
5. Subcutaneous LD_{50} (rat)	EPA Accession No. 94683
6. Intraperitoneal (rat)	EPA Accession No. 94683
7. 21-Day Subacute Dermal (rabbit) (Roundup)	EPA Accession No. 94176

II. Subacute, Chronic and Delayed Toxicology Studies

EPA Accession No. 94683

1. 21-day Subacute Dermal (Rabbit)	NEL 2000 ppm
2. 90-day Subacute Oral (Rat) (Beagle dog)	NEL 2000 ppm
3. Mutagenic (mouse dominant-lethal, 10 mg/kg:	negative
4. Carcinogenic mouse (18 mon.)	NEL 300 ppm
5. Teratogenic (Rabbit)	negative at 30 mg/kg
6. Reproduction (Rat)	NEL 100 ppm
7. 2-Year Chronic Oral (Beagle Dog):	NEL 300 ppm
8. 2-Year-Chronic Oral (Rat)	NEL 100 ppm
9. ChE Inhibition (Rat)	Negative
10. Neurotoxicity (Chicken)	Negative

B. Toxicology Data Submitted

Acute Toxicology Studies

1. Toxicity Studies on 60% WSP 1.5 Na-glyphosate (Younger Laboratories, project no. Y-77-16, Feb. 18, 1977)

Test Material: 60% WSP 1.5 Na-glyphosate, XHH-214

a. Acute Oral Toxicity

One group of 5 Sprague-Dawley Rats (2M & 2F) received a single dose of 10,000 mg/kg of test material. Observation for 14 days.

Results: no deaths LD_{50} >10,000 mg/kg (both sexes)

Necropsy: Viscera appeared normal

Toxic Sign: reduced appetite for one day

Classification: Core-Minimum Data TOX Category IV: CAUTION

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b. Acute Dermal Toxicity

Two groups (low dose- 1 male; high dose - 1 male, 1 female) received dermally on intact fur clipped skin doses of 5,010 mg/kg and 7,940 mg/kg for 24 hours under an imprevious cuff. Observation for 14 days.

Results: no deaths in the 3 rabbits

Toxic Sign: reduced appetite for three days

Necropsy: Viscera appeared normal

Body weight: not recorded

Classification: Supplementary Data (a) not enough animals were tested (b) abraded skin was not noted.

TOX Category III: CAUTION

c. Acute Eye Irritation

0.1 ml of test material was instilled into one eye of each of six rabbits with the untreated eye serving as control. Observation at 1, 24, 48, 72, 5 and 7 days.

Results: No corneal opacity, slight to moderate conjunctivitis. All scored zero at 48 hours.

Classification: Core-Minimum Data TOX Category III: CAUTION

d. Primary Skin Irritation

0.5 gm applied to six rabbits as finely ground sample moistened with water according to FHSA. Observation at 4, 24, 48, 72 and 7 days. P.I. = 6.5 at 72 hours

Results: Severe defatting effect persisted up to 72 hours. Skin sloughed off in 14 to 72 hours. There was no injury in depth.

Classification: Core-Minimum Data TOX Category II: WARNING

B. 1. Referenced petitions: EPA Accession No. 94176, 94683, PP#6G1862

2. Established tolerances. 40 CFR 180.364

Tolerances are established for glyphosate and its metabolite in or on the following racs.

grain hops: 0.1 ppm (N)
grass, forage: 0.1 ppm (N)
soybeans: 0.2 ppm (N)
soybean, forage: 0.4 ppm
soybean, hay: 0.4 ppm (see computer printout)

3. Pending Tolerances

PP8G2051, 8F2070, 7F2016, 7F1971, 6F1861, 6H5144, 6E1809, 6F1733 (See computer printout)

These pending tolerances will used up 4.5% of the ADI.

C. Calculation of the ADI

The ADI is based on the NOEL of 100 ppm.in a 2 year rat study (most sensitive species). This NOEL equals 5.0 mg/kg/day. A safety factor of 100 is used to calculate the human ADI.

ADI = 5.00 mg/kg/day X $\frac{1}{100}$ = .05 mg/kg/day

The MPI for a 60 kg person consuming a diet of 1500 gm is:

MPI = 60 kg X .05 mg/kg/day = 3.00 mg/person/day

The published 40 CFR 364 tolerances for glyphosate will use up 0.78% of the ADI. Unpublished, Toxicology Branch approved tolerances (PP5G1561, 6G1679, 6G1734, 6G1757, 6G1826, 6G1862, 7G1893, 8G2020 and 8G2032) will use up 8.09% of the ADI. These previous actions will use up 8.87% of the ADI.

The current action will use up an additional 4.56% of the ADI. The total of previous actions and the current action will use up 13.43% of the ADI.

Other pending tolerances (8.3.) will use up 4.5% of the ADI. Therefore, the total of all previous, current and oending actions on glyphosate will use up 17.93% of the ADI. (See computer printout)

D. Conclusion and Recommendations:

Toxicology Branch finds that the EUP and the requested temporary tolerances adequately supported by available toxicology data on glyphosate. The total contribution of all previous, current and pending actions on glyphosate will use up only 17.93% of the ADI. It should be noted that most supporting studies (Subacute, Chronic, Reproductive, teratology, carcinogenicity, and mutagenicity) on glyphosate are from Industrial Bio-Test. These studies have to validated or repeated. Prior to registration, the questions and criticisms in this and previous reviews must be addressed by the registrant, since Toxicology Branch in the past has recommended against registration of the establishment of permanent tolerances for glyphosate.

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RD initial G.E.W. 4/12/78

E for GEW. 4/12/78

Glyphosate: 8G2060, 8H5179

Type on to TOX Review as page 6.

Chemistry Branch Considerations:

The nature of the formulations used in field studies has not been identified. Pending resolution of this deficiency, the tentative conclusion is made that the temporary tolerances are adequate in conjunction with the proposed use. Either residue data (and suitable tolerance proposals) or appropriate labeling restriction feed use needs to be submitted for sugarcane fodder and forage. Pending resolution of the feeding restriction or residue data for sugarcane fodder, RCB can draw only a tentative conclusion that the proposed 0.1 ppm temporary tolerance for combined residue in liver and kidney will be adequate. In light of RBC memo of 9/22/78 from M. Nelson, Toxicology Branch recommendations are tentative until resolution of the deficiences of RCB are completed.

10/12/78